TAB D

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

October 7, 1992

Glaxo Inc.
Five Moore Drive
P.O. Box 13358
Research Triangle, N.C. 27709

Dear Dr. Curnow:

Thank you for your April 15, and May 21, 1992, letters regarding the standards required of your approved NDA for Ventolin Nebules (albuterol sulfate inhalation solution) versus those approved in the ANDA for Dey Laboratories Inc. for the same drug and dosage form. I welcome your comments and insights into the drug review and approval processes and the opportunity to improve the process through meaningful dialogue and interchange with all interested parties.

As stated in my interim response dated May 11, 1992, because the applications were approved by two different CDER groups, the Office of Drug Evaluations I and Generic Drugs, I needed to seek information from both of the offices regarding the issues raised in your letters before I was able to more fully respond to your concerns. I appreciate your providing detailed scientific information on albuterol sulfate. This information has served as the focal point for discussion among Center staff.

Before commenting specifically on the issues raised by you about your and Dey's products, allow me to describe our goals and procedures in their review and regulation. Our goal is to achieve substantial uniformity of standards and consistency of review among the various review divisions and across offices within the Center. Communication between scientific professionals directly involved in the review process is a key element in achieving this goal. The concerns identified in your letters have sensitized the review staff to the critical need for scientific exchange between the offices. To facilitate communication and exchange of information, the Offices of Drug Evaluation and Generic Drugs have established a regular schedule of scientific and administrative meetings to discuss issues of concern arising during the review process. In addition, supervisory staff in the Office of Generic Drugs have emphasized that reviewers of generic drug applications should pay particular attention to differences from the listed drug and discuss any differences before taking action.

other ongoing efforts to accomplish the objective of substantial uniformity of standards and consistency of review include the systematic review and updating of existing guidelines and development of new guidelines and statements of policy to facilitate the submission and review of applications. We also have an active education and training program for review staff to foster development and maintenance of technical and regulatory expertise.

I am committed through these ongoing activities to achieve the goal of substantial uniformity of standards and consistency of review among the various review divisions and across offices within the Center. If you have any suggestions on how to further this effort, I encourage you to provide your ideas.

In response to the specific issues raised in your letters referenced above, the Center intends to require that all manufacturers of inhalation products used to treat asthma ensure that their formulations do not contain excipients not contained in the listed drug such as EDTA, benzalkonium chloride, or sulfites.

The Center also intends to require that all manufacturers of products packaged in low density polyethylene (LDPE) containers: 1) use a secondary overwrap, such as a laminated foil, to insure the identity, strength, quality and purity of the drug product; or 2) demonstrate that such an overwrap is unnecessary. Manufacturers of products packaged in LDPE containers will be asked to give particular consideration to the use of an overwrap to control water vapor permeation, gas permeation, extractables and leachables (including adhesives and ink from labeling).

We appreciate your willingness to share information from your NDA about the method(s) used to identify vanillin or other impurities/ degradants with other firms marketing albuterol sulfate solution for inhalation. Would you also be willing to share the data you generated on your product? We encourage you to work with USP in developing a drug product monograph for Albuterol Solution for Inhalation that would set limits on toxic impurities and degradants.

Thank you once again for bringing to our attention these challenging issues.

Sincerely,

Carl C. Peck, M.D.
Director,
Center for Drug Evaluation and Research